REMARKS

The applicant notes with appreciation that the rejections under section 102(e) to claims 29, 30, 32, 33, 40, and 44 have been withdrawn.

The applicant kindly requests that US Patent 5,599,708 (Mundy et al.), which was cited in the Office action dated November 26, 2003, be entered on the list of cited references.

Status of the Claims

Claims 29-33, 35-41, 43-48, and 55-57 remain in the application. Claims 34, 42, 49-54 have been canceled. Claims 1-28 have been withdrawn.

Summary of the Amendments

Independent claim 29 and its dependent claims have been amended to clarify that the nucleic acid molecules in the claims are oligonucleotides. Support for this amendment comes from the specification at page 10, lines 5-7, 8, & 22, for example.

Claim 29 has also been amended to clarify that the hybridization domains on both the first and second oligonucleotides consist of sequences of about 5 to about 10 nucleotides. Support for this amendment can be found at page 19, line 6 of the specification.

With respect to the first oligonucleotide of claim 29, the claims have been amended to clarify that the Substrate Hybridization Domain adjoins the Signal Template Domain. Support for this amendment can be found in the specification in Fig. 1 at "A)ii)" where this configuration is shown diagrammatically. Additional support can be found at page 22, lines 1-6.

With respect to the second oligonucleotide of claim 29, the claims have been amended to clarify that the Template Hybridization Domain adjoins the Target Binding Domain. Support for this amendment can be found in the specification in Fig. 1 at "A)i)" where this configuration is shown diagrammatically. Additional support can be found at page 21, lines 31-36.

Claim 29 has been further amended to clarify that an oligonucleotide having from 5' to 3' an unlabeled Target Binding Domain adjoining a Template Hybridization Domain adjoining a labeled Signal Domain is created. Support for this amendment can be found at Fig. 1 at C).

Claim 29 has been further amended to delete the phrase "having a sequence which shows complementarity toward and is hybridizable to the Signal Template Domain." This phrase is considered redundant because it describes an end result of the method.

Claim 31 has been amended for grammatical reasons, it is not believed that the amendment changes the content in the claim, nevertheless, support for the claim can be found at page 18, line 17-20.

Claim 39 has been amended to change its dependency so that it will depend from claim 29. It is believed this claim, as originally filed, was dependent on claim 29 and its dependency was inadvertently changed to claim 37 during prosecution. The amendment is intended to return the claim to its original and intended form.

Claims 49-54 have been canceled.

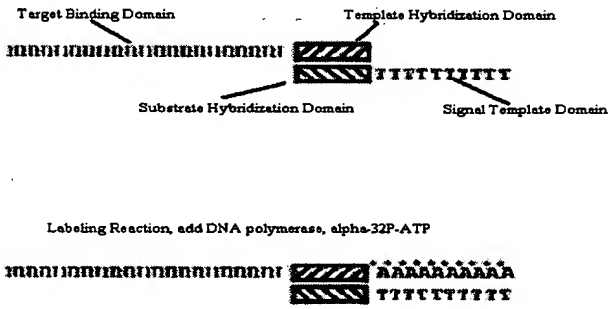
New independent claim 58 has been added to the application. Claim 58 is identical to currently amended claim 29 with the exception that limitations requiring that the Target Binding Domain and Template Hybridization Domain not be detectably labeled in claim 29 are absent in claim 58.

Summary of the Invention

The invention is for a general method of labeling the 3' end of oligonucleotides with a defined number of detectable markers. The method produces a more uniform labeled oligonucleotide product and several-fold higher levels of marker incorporation than has previously been available.

The method involves annealing two oligonucleotides together through short hybridization domains that consist of less than 10 nucleotides. The oligonucleotides include a hybridization probe (termed a "Substrate Nucleic Acid" in the application) and a template (termed a "Template Nucleic Acid"). The template defines which nucleotides to add to the hybridization probe and the number of additions. The hybridization probe contains a short sequence of less than 10 nucleotides, such as GGCGGG, added toward its 3'-end (termed a "Template Hybridization Domain") to facilitate hybridization with the template through the template's hybridization domain (termed a "Substrate Hybridization Domain"). The region of the template oligonucleotide that serves as a template for the addition of nucleotides containing the detectable marker (i.e. α-^{32}P phosphate) to the 3'-end of the hybridization probe is usually a sequence of T nucleotides. This region is designated as the "Signal Template Domain." Following the

annealing step, nucleotides containing detectable labels or markers are incorporated onto the 3' end of the hybridization probe using a DNA polymerase, such as the Klenow fragment. The terminology and method are diagramed below.



Specification Objection

The specification has been amended by deleting the noncompliant pages to correct the informalities noted by the Examiner in paragraphs 1 & 2 of the Office action.

Claim Objections

The claims have been amended by deleting independent claims 49-51 and their dependent claims 52-54 to correct the objection noted by the Examiner in paragraphs 3 & 4 of the Office action.

Section 112 Claim Rejections

The applicant submits that the Hybridization Domains which, in the currently amended claims, now consist of sequences of about 5 to about 10 nucleotides now meet the written description requirement. Support for this amendment can be found at page 19, line 6 of the specification.

Rejections to claims 51-54 are now moot as those claims have been canceled in order to obtain prompt issuance of the application.

Section 103 Claim Rejections

The Office action rejected unamended claim 29 as obvious over US Patent 5,882,856 to Shuber in view of US Patent 5,710,028 to Eyal et al. Claim 29 was interpreted as encompassing a "Substrate Hybridization Domain" and a "Template Hybridization Domain" which each consist of as few as 1 nucleotide and as encompassing a "first nucleic acid" and a "second nucleic acid" that are each of virtually any length. Unamended claim 29 was also considered to encompass any number of additional nucleotides at any location in the first and second nucleic acids.

Shuber discloses a PCR assay that uses a DNA primer that is said to be particularly useful for multiplexed reactions. The Office action states, at paragraph 23, that Shuber discloses a chimeric primer corresponding to applicants' first sequence which is configured as 5'-XY-3.' The "X" domain is said to meet the limitations of applicants' Signal Template Domain and the "Y" domain is said to meet the limitations of applicants' Substrate Hybridization Domain. Shuber discloses that the 3'-"Y" sequence comprises 17-25 bases. (Col. 2, lines 60-64) The Office action also takes the position that Shuber's target sequence meets the limitations of applicant's second nucleic acid sequence. Shuber's target sequence is DNA extracted from a variety of biological sources including eukaryotic, prokaryotic and viral sources and is suitable for PCR amplification. (Col 5, lines 23-40).

As currently amended, claim 29 now requires two oligonucleotides that hybridize to each other. Each oligonucleotide has a Hybridization Domain that consists of sequences that are about 5 to about 10 nucleotides in length. Claim 29 also now requires that, with respect to the first oligonucleotide, the Substrate Hybridization Domain adjoins the Signal Template Domain and, with respect to the second oligonucleotide, the Template Hybridization Domain adjoins the Target Binding Domain. The term oligonucleotide is defined in the specification, consistently with its meaning in the art, as "single stranded nucleic acid molecules that are relatively short, generally no longer than about 150 nucleotides." See page 10, lines 5-7.

The method of presently amended claim 29 distinguishes over Shuber in numerous ways. For example, Shuber completely lacks a second oligonucleotide as is now required by amended claim 29. As a result Shuber also cannot meet the limitation of amended claim 29 requiring "hybridizing a first oligonucleotide to a second oligonucleotide." In addition, claim 29 now requires the first oligonucleotide to have a Substrate Hybridization Domain that consists of a sequence of about 5 to about 10 nucleotides. In contrast, Shuber's corresponding 3'-"Y" sequence comprises 17-25 bases.

Claim 29 also now requires a second oligonucleotide that comprises from 3' to 5' a Target Binding Domain that comprises a nucleotide sequence "heterologous" to that of the Template Hybridization Domain. The term heterologous in this context means that the Target Binding Domain sequence "does not follow the Target Binding Domain in its native context." (Page 10, lines 24-30) This requirement distinguishes over Shuber's target sequences which are genomic DNA extracts, *i.e.,* solely DNA "in its native context." Again, Shuber's genomic DNA extracts are not oligonucleotides as required by amended claim 29.

Amended claim 29 also requires extending the second oligonucleotide with a DNA polymerase. In Shuber, the chromosomal DNA nucleic acid sequence (which is purported in the Office action to correspond to the second oligonucleotide) is not extended or even extendable, rather the oligonucleotide primer in Shuber (which is purported in the Office action to correspond to the first oligonucleotide) is extended in Shuber's PCR amplification reactions.

The applicant respectfully submits that Eyal et al. is so lacking with respect to the limitations of presently amended claim 29 that it cannot be combined with Shuber et al. in a way to overcome the deficiencies in Shuber as noted above.

Eyal et al. discloses methods for identifying point mutations using primer extension reactions in which only a single nucleotide is added. As in Shuber, Eyal et al. completely lacks a second oligonucleotide as required by claim 29 and also fails to meet the limitation of presently amended claim 29 requiring "hybridizing a first oligonucleotide to a second oligonucleotide." In addition, the oligonucleotide primer disclosed in Eyal et al. lacks a "heterologous" nucleotide sequence as required by claim 29. Rather, a primer sequence that is complementary to the genomic sequence being tested is disclosed. (Col. 3, lines 25-26; col. 3, lines 55-57).

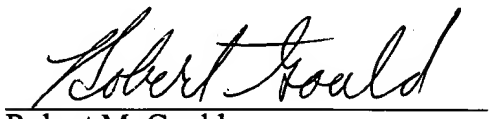
In summary, neither Shuber nor Eyal et al. use an oligonucleotide template to prime their respective extension reactions. Neither reference meets the limitation requiring "hybridizing a first oligonucleotide to a second oligonucleotide" and neither reference discloses a second oligonucleotide with a "heterologous" nucleotide sequence. Consequently, even if sufficient motivation exists to combine these references, the references do not anticipate and cannot make obvious the limitations of claim 29.

Conclusion

The application is considered in good and proper form for allowance, and the examiner is respectfully requested to pass this application to issue. If, in the opinion of the examiner, a

telephone conference would expedite the prosecution of the subject application, the examiner is invited to call the undersigned attorney.

Respectfully submitted,



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Date: February 26, 2004

CERTIFICATE OF MAILING

I hereby certify that this Amendment and the documents referenced as being concurrently submitted and/or resubmitted are being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to:

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

on February 26, 2004.

Typed or printed name of person signing this certificate:

Robert Gould

Signature /Robert Gould/